

## AMENDMENTS TO THE SPECIFICATION

Please rewrite paragraph 0041 on page 4 of the published application as follows:

Preferred chromatin inactivation portions are described in the Examples, and include a polypeptide/polypeptide mimic or analogue derivable from SAP18 with the amino acid sequence (SEQ ID NO:1) XXXMAVESRVTQEEIKKEPEKPIDREKTCPLLLRVF (where XXX is, for example, a AAA or DDD linker, or other hydrophilic, preferably charged linker) and a polypeptide derivable from MAD1 with the amino acid sequence (SEQ ID NO:2) XXXMNIQMLLEAADYLERREREAEHGYASMLP (where XXX is, for example, a AAA or DDD linker, or other hydrophilic, preferably charged linker).

Please rewrite paragraph 0049 on page 4 of the published application as follows:

The molecule may further comprise a portion which facilitates cellular entry and/or nuclear localisation (locating portion). This portion may also be a polypeptide or polypeptide mimic/analogue. For example, the locating portion may comprise or consist of a peptide with membranotropic activity as discussed, for example, in Soukchareun *et al* (1998) *Bioconjugate Chem* **9**, 466-475 and references cited therein, for example Soukchareun *et al* (1995) *Bioconjugate Chem* **6**, 43-53 (viral fusion peptides) or Eritja *et al* (1991) *Tetrahedron* **47**, 4113-4120 (nuclear transport signal sequences). It may be a nuclear localisation signal peptide (for example (SEQ ID NO:3) DDDPKKKRKV-NH<sub>2</sub>) or endosomal lytic peptide (which may facilitate release of the molecule from the endosomal compartment) mentioned in WO 99/13719. It is preferred that this portion is of less than 3 kDa, preferably of less than 2.5 kDa. It is preferred that the total polypeptide/mimic/analogue content of the molecule is less than 11 kDa. Typically, a localisation

portion may have between about 7 and 16 amino acids.

Please rewrite paragraph 0050 on page 4 of the published application as follows:

Further examples of localisation portions include modified Antennapedia homeodomain based Penetratins (for example (SEQ ID NO:4) RQIKIWFQNRRMKWKK), or TAT (for example (SEQ ID NO:5) C(Acm)GRKKRRQRRRPPQC, where C(Acm) is a Cys-acetamidomethyl) or VP22 based molecules (Prochiantz (2000) *Curr Opin Cell Biol* **9**, 420-429).) or basic HIV TAT internalisation peptide.

Please rewrite paragraph 0149 on page 11 of the published application as follows:

The TFO sequences for BclP and BclU are (5' to 3'):

BclP

(SEQ ID NO:10) GGGTGTGGGGTUTGTGTGTGGT

BclU

(SEQ ID NO:11) GGTGTUTTGGTTGGGTGT

Please rewrite paragraph 0156 on page 12 of the published application as follows:

As an example, the TFO is designed to form a triplex with the Bcl-2 promoter region (see accession nos: NM\_000657 and NM\_0006333). The selected region is very purine rich on one DNA strand and is, therefore, a candidate sequence for forming a DNA triplex by H $\ddot{o}$ ogsteen base pairing. The rules for designing potential TFO are summarised in: Vasquez KM and Wilson JH, Trends Biochem Sci, 1: 4-9, 1998. The sequence (SEQ ID NO:10)

(5'GGGTGTGGGGTUTGTGTGTGGT3' (BclP) or (SEQ ID NO:12))

5'TUGTGTGGGTGTGGTGUGGG3' or (SEQ ID NO:11)

5'GGTGTUTTGGTTGGGTGT3' (BclU)) was produced as an oligonucleotide (Module 1) with an activated 5' end for chemical coupling to Module 2 peptides. Module 2 peptides explored in this study include human MAD1 transcriptional repressor domain (for example amino acids (SEQ ID NO:2)

XXXMNIQMLLEAADYLERREREAEHGYASMLP (where XXX is, for example, a AAA or DDD linker)). The latter is a region known to interact with the histone deacetylase complex protein Sin3a.

Additionally, we have explored the use of amino acids (SEQ ID NO:1) XXXMAVESRVTQEEIKKEPEKPIDREKTCPLLLRVF (where XXX is, for example, a AAA or DDD linker) of the human Sap18 protein, also known to associated with Sin3a protein. This region corresponds to a sequence of high evolutionary conservation and overlaps with a region that can mediate gene repression. Module 2 peptides were synthesised in an activated form to enable subsequent coupling to the activated Module 1 oligonucleotide by "native ligation" chemistry (see WO 01/15737 and Stetsenko & Gait (2000) *Organic Chem* **65(16)**, 4900-4908), in which an N-terminal thioester-functionalised peptide is coupled to a 5'-cysteiny1 oligonucleotide.

Please rewrite paragraph 0165 on page 13 of the published application as follows:

Endogenous gene regulation is measured, for example by assessing transcription of the gene (for example using PCR) or by assessing the quantity or activity of the encoded polypeptide. In an example, the oligonucleotide is directed to the Bcl-2 gene regulatory site. Examples of suitable RT-PCR primers include

(SEQ ID NO:13) 5' TCCGGTATTTCGAGAAGTCC 3'

(SEQ ID NO:14) 5' ATCAGAAGAGGATTCCTGCC 3'

(used to assess BclP)

and

(SEQ ID NO:15) 5' TGATGGAGCTCAGAATTCC 3'

(SEQ ID NO:16) 5' TGCCTCTCCTCACGTTCC 3'

(used to assess BclU).

Please rewrite paragraph 0227 on page 16 of the published application as follows:

which has the amino acid sequence:

(Link) (SEQ ID NO:17) DDDMNIQMLLEAADYLERREREAHGYASMLPDDDPKKKRKV  
(carboxamide)

Please rewrite paragraph 0229 on page 16 of the published application as follows:

which has the amino acid sequence:

(Link) (SEQ ID NO:18) DDDPKKKRKVDDDMNIQMLLEAADYLERREREAHGYASMLP  
(carboxamide)

Please rewrite paragraph 0230 on page 16 of the published application as follows:

The NLS is a 7 amino acid (sequence (SEQ ID NO:19) PKKKRKV) functional nuclear localisation signal derived from the SV40 T-antigen.

Please rewrite paragraph 0235 on page 16 of the published application as follows:

Bcl2 is the TFO oligo sequence shown in Example 8

(SEQ ID NO:10) (5'GGGTGTGGGGTUTGTGTGTGGT3'

or

(SEQ ID NO:12) 5'TUGTGTGGGTGTGGTGUGGG3'

or

(SEQ ID NO:11) 5'GGTGTUTTGGTTGGGTGT3').